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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,783	12/24/2001	Michael Graupe	1016US	3968

5487 7590 02/02/2005

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EXAMINER	
SHIAO, REI TSANG	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 02/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,783	GRAUPE ET AL.	
	Examiner	Art Unit	
	Robert Shiao	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *RCE of 10/035,783 filed on 12/08/04* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *01/04/05* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This application claims benefit of the provisional application:

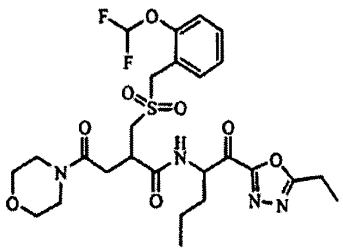
60, 257,603 with a filing date 12/22/2000.

2. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 08, 2004, has been entered.

3. Amendment of claims 1-28, cancellation of claims 30-31 in the amendment filed on December 08, 2004, is acknowledged. Claims 1-29 are pending in the application.

Responses to Election/Restriction

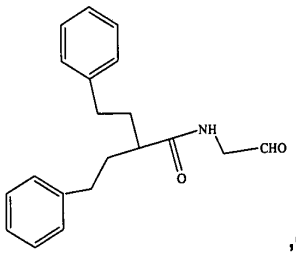
4. Applicant's election of restriction requirement II with traverse of Group I claims 1-28, in part, in the amendment dated March 29, 2004, is acknowledged. A compound 2-(2-difluoromethoxy-benzylsulfonylmethyl)-N- [1-(5-ethyl [1,3,4] oxadiazole-2-carbonyl) butyl] 4-morpholin-4-yl-4-oxo butyramide of the formula

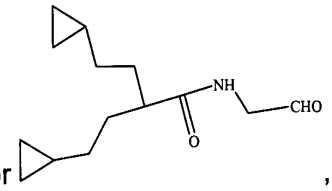


, has been elected as a single species. The

traversal is on the grounds that the Examiner has not offered any explanation of restriction requirement II, and *In re Harnish* and *Ex parte Hozumi* are cited. This is not found persuasive and reasons are given, *infra*.

Status of the Claims

5. It is noted that it is impossible for the examiner to discover instant formula (I) without limiting the number of compounds to be considered via a proper restriction requirement. The simplest compound encompassed by the claims appears to be $(H_2NCH_2)_2CH\text{-}C(O)\text{-}NH\text{-}CF_2CHO$, 

,or 

, which includes the CH-C(O)-NH- core. Many more complicated structures, including many with heterocyclic rings are encompassed by the generic structure of claim 1 and have no relationship with or apparent common activity with this simplest compound. Applicants' claims are especially confusing as all of the three main variables are defined by a second set of variables which include further variables which include additional variables, see petition decision, dated December 3, 2003, page 3, lines 11-17.

6. Claims 1-29 are pending in the application. The scope of the invention of the elected subject matter is as follows:

Claims 1-28, in part, drawn to compounds/compositions of formula (I) having

variables X_1, R^3, and R^4, X_1 represents $-C(R^1)(R^2)X^2$, wherein X^2 is as defined in claim 1, wherein hetero(C_4-C_{10})aryl or hetero(C_4-C_{10})cycloalkyl of X^2 represents pyran, thiopyran, pyrimidine, thiazole, isothiazole, pyridine, furan, imidazole, isoxazole, oxadiazole, oxazole, or triazole thereof; $R^1$and R^2 are as defined in claim 1, except: $R^1$and R^2 independently do not represent heteroaryl, heterocycloalkyl, or heterocycloalkylene or $R^1$and R^2 independently is not substituted with heteroaryl, heterocycloalkyl, or heterocycloalkylene, $R^1$and R^2 taken together with the carbon atom do not form hetero(C_3-C_8)cycloalkylene; **R^3** represents $-C(R^{16})(R^{17})X^7$, R^{16} and R^{17} independently represent hydrogen, alkyl, fluoro, or hydroxy; X^7 is as defined in claim 1 except: X^7 do not represent heteroaryl, heterocycloalkyl, or heterocycloalkylene, and X^7 is not substituted with heteroaryl, heterocycloalkyl, or heterocycloalkylene; and **R^4** represents $-C(R^{16})(R^{17})X^7$, R^{16} and R^{17} independently represent hydrogen, alkyl, fluoro, or hydroxy; X^7 of **R^4** represents $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4NC(O)NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$, or $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, and X^4 represents a bond or alkylene, R^{12} represents hydrogen or alkyl, R^{15} of R^4 does not represent (C_3-C_{10})cycloalkyl(C_0-C_6)alkyl, (C_6-C_{10})aryl(C_0-C_6)alkyl, (C_9-C_{12})bicycloaryl(C_0-C_6)alkyl, hetero(C_5-C_{10})aryl(C_0-C_6)alkyl or hetero(C_8-C_{12})bicycloaryl(C_0-C_6)alkyl, and wherein the hetero(C_3-C_{10})cycloalkyl of R^{15} represents **morpholinyl** thereof, and X^7 is not substituted with heteroaryl, heterocycloalkyl, or heterocycloalkylene. **It is noted that the variable R^3 does not have morpholine moiety.**

The above mentioned withdrawn compounds which are withdrawn from consideration as being for non-elected subject matter differ materially in structure and composition from the compounds of the elected invention. The withdrawn compounds contain varying functional groups (i.e., heterocyclic or heteroaryl) which differ from those of the elected invention such as azepane, piperidine, pyran, piperazine, morpholine, pyridazine, pyrimidine, thiazole, oxazole, etc, which are chemically recognized to differ in structure and function. This recognized chemical diversity of the functional groups can be seen by the various classification of these functional groups in the U.S. classification system, i.e., class 540 subclass 484(+) (azepane), class 546 subclass 184(+) (piperidine), class 549 subclass 200(+) (pyran), class 544 subclass 358(+) (piperazine), class 544 subclass 106(+) (morpholine), class 544 subclass 224 (+) (pyridazine), class 544 subclass 242 (+) (pyrimidine), class 548 subclass 146(+) (thiazole), class 548 subclass 215(+) (oxazole), etc. Therefore, again, the compounds which are withdrawn from consideration as being for non-elected subject matter differ materially in structure and composition and have been restricted properly.

The Markush group set forth in the claims includes both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. For these reasons provided below, restriction to one of the following Groups is required under 35 U.S.C. 121, wherein an Group is a set of patentably distinct

inventions of a broad statutory category (e.g. Compounds, Methods of Use, Methods of Making, etc.).

Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

The invention claims 1-28, in part, embraced in above elected subject matter are prosecuted in the case. Claims 1-28, in part, not embraced in above elected subject matter, and claim 29, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The restriction requirement is still deemed proper and is therefore made FINAL.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

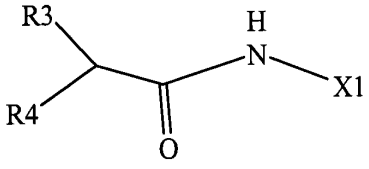
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

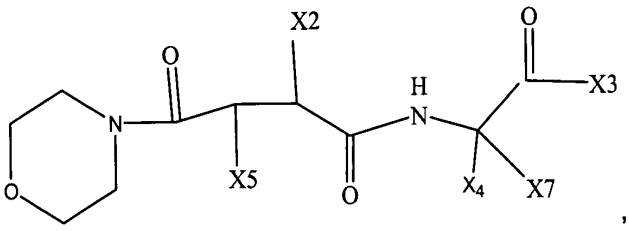
8. Claims 1-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 13 of Graupe et al. copending Application No.10/183,128. Although the conflicting claims are not identical, they are not patentably distinct from each other and reasons are as follows.

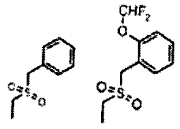
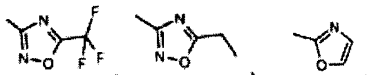
Applicants claim a compound of formula I as cathepsin inhibitors,



, wherein X^1 is $-C(R^1)(R^2)X^2$, and R^1 is hydrogen, R^2 is C_{1-6} alkyl, X^2 is $-C(R^7)(R^8)R^5$, and R^7 and R^8 together form oxo, and R^5 is hetro(C_{4-10})aryl(C_{0-6})alkyl, i.e., thiazole, oxadiazole; R^3 is $-C(R^{16})(R^{17})X^7$, R^{16} and R^{17} independently are hydrogen, hydroxy, or alkyl, X^7 is $-X^4S(O)_2R^{15}$, and X^4 is a bond, R^{15} is (C_{3-10}) cycloalkyl (C_{0-6})alkyl or (C_{6-10}) aryl (C_{0-10})alkyl, and R^4 is $-C(R^{16})(R^{17})X^7$, both R^{16} and R^{17} are hydrogen, X^7 is $-X^4C(O)R^{15}$, and X^4 is a bond, R^{15} is morpholinyl. A compound 2-(2, difluoromethoxy-benzylsulfonylmethyl)-N-[1-(5-ethyl[1,3,4]oxadiazole-2-carbonyl)butyl]-4-morpholin-4-yl-4-oxo butyramide has been specifically exemplified in the specification. The compound is found on the pages 2-10 of the specification.

Graupe et al. '128 claim a compound of the formula as cathepsin inhibitors,



, wherein X^2 is sulfonyl alkyl motif. i.e.,  ; X^3 is heterocycle motif, i.e.,  or  ; X^5 is hydrogen, OH, or –O-R, and R is a straight or branch alkyl containing 1-6 carbon atoms; X^4 and X^7 are independently hydrogen or –R, and R is a straight or branch alkyl containing 1-6 carbon atoms. Claims 18-19 read on the compounds of claim 13. The compound is found on the pages 2-14 of the specification.

The difference between Graupe et al. '128 and instant claims is that variables X_4 of the formula of Graupe et al. represents alkyl group, while variable R^1 of instant claim, which is an equivalent variable to X_4 of Graupe et al. '128, is hydrogen.

One having ordinary skill in the art would find the instant claims 1-28 prima facie obvious **because** one would employ the compound of Graupe et al., wherein X^1 is $-C(R^1)(R^2)X^2$, and R^1 is hydrogen, R^2 is C_{1-6} alkyl, X^2 is $-C(R^7)(R^8)R^5$, and R^7 and R^8 together form oxo, and R^5 is hetro(C_{4-10})aryl(C_{0-6})alkyl, i.e., thiazole, oxadiazole; R^3 is $-C(R^{16})(R^{17})X^7$, R^{16} and R^{17} independently are hydrogen, hydroxy, or alkyl, X^7 is $-X^4S(O)_2R^{15}$, and X^4 is a bond, R^{15} is (C_{3-10}) cycloalkyl (C_{0-6})alkyl or (C_{6-10}) aryl (C_{0-10}

)alkyl, and R^4 is $-C(R^{16})(R^{17})X^7$, both R^{16} and R^{17} are hydrogen, X^7 is $-X^4C(O)R^{15}$, and X^4 is a bond, R^{15} is morpholinyl.

The motivation to make the claimed compounds derives from the expectation that the instant claimed compounds would possess similar activities, i.e., cathepsin inhibitors, from the known Graupe et al. compounds to that which is claimed in the reference.

Objection

9. Claims 1-28 are objected to as containing non-elected subject matter, i.e., the variable R^3 of claims 1, 4 does not have heteroaryl, heterocycloalkyl, or heterocycloalkylene, R^{15} of R^4 does not represent $(C_3\text{-}C_{10})$cycloalkyl$(C_0\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_0\text{-}C_6)$alkyl, $(C_9\text{-}C_{12})$bicycloaryl$(C_0\text{-}C_6)$alkyl, piperazine of claim 5, heteroarylalkyl of R^2 of claims 6-7, compounds of claim 9, limitation of variable R^5 of claims 11-12, 14-15, variables R^5 and R^6 of claims 23-24, and 27 together not forming a ring, the formula of claims 25-26 does not have the variable X^3, and claim 29, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on pages 3-4 *supra*.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/31/05

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January 31, 2005